PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2005/000562	International filing date *(day/month/year)* 18.01.2005
Priority date *(day/month/year)* 22.01.2004	
International Patent Classification (IPC) or both national classification and IPC C07K14/195, C12N15/31, C07K16/12, C12Q1/68, A61K39/02	
Applicant AKZO NOBEL N.V.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Hix, R Telephone No. +31 70 340-3898

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1, 10-14, 23-32

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 10-14, 23-32
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1, 10-14, 23-32
Industrial applicability (IA)	Yes:	Claims	1, 10-14, 23-32
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item IV

Lack of unity of invention

The separate inventions/groups of invention are:

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 2: Claims 2 and 15 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 27kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 3, protein that is at least 90% homologous to SEQ ID NO: 4, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 3: Claims 3 and 16 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 62kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 5, protein that is at least 90% homologous to SEQ ID NO: 6, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 4: Claims 4 and 17 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 57kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic

acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 7, protein that is at least 90% homologous to SEQ ID NO: 8, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 5: Claims 5 and 18 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 74kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 9, protein that is at least 90% homologous to SEQ ID NO: 10, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 6: Claims 6 and 19 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 44kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 11, protein that is at least 90% homologous to SEQ ID NO: 12, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 7: Claims 7 and 20 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 43kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 13, protein that is at least 90% homologous to SEQ ID NO: 14, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 8: Claims 8 and 21 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 26/31kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 15, protein that is at least 90% homologous to SEQ ID NO: 16, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 9: Claims 9 and 22 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 101kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 17, protein that is at least 90% homologous to SEQ ID NO: 18, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

The general concept of characterizing nucleic acids which encode *Lawsonia intracellularis* proteins as using them in vaccines against *Lawsonia intracellularis* is already known from the prior art document D1: EP-A-1 219 711 (Akzo Nobel N.V.) and D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)

D1 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D2 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.

Due to the fact that the common unifying concept is known in the state of the art, there appears therefore to be no technical features in common between the different inventions involving different nucleotide and amino acid sequences, that could provide a novel and inventive unifying concept.

Consequently, the requisite unity of invention (Rule 13.1 PCT) therefore

no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the groups of claims.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Examination of :

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

1 The following **documents** are referred to in this communication; the numbering will be adhered to in the rest of the procedure:
D1: EP-A-1 219 711 (Akzo Nobel N.V.)
D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)

2 **NOVELTY** (Art. 33(2) PCT)

2.1 In view of the prior art cited, claims 1 and 14 and claims dependent thereon appear to be novel and meet therefore the requirements of Art.33(2) PCT, since

the nucleic and amino acid sequences SEQ ID NOs: 1 and 2 are not disclosed in the state of the art.

3 **INVENTIVE STEP** (Art. 33(3) PCT)

3.1 Documents D2 and D3 are considered to represent the most relevant state of the art. D2 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D3 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.

3.2 The subject-matter of the present application and claims 1 and 14 and claims dependent thereon involve different nucleic acid sequences and their use as immunogenic fragments as vaccines against *Lawsonia intracellularis*.

3.3 The problem may be defined as the provision of alternative nucleic acid sequences and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*.

3.4 However due to the fact that the above problem has previously been solved by the subunit vaccines of the state of the art and that there is no evidence in the description that the nucleic or amino acid sequences SEQ ID NOs: 1 and 2 actually solve the problem through initiating an effective protective immune response to *Lawsonia intracellularis*, the subject-matter of claims 1 and 14 cannot be recognized as involving an inventive step according to Article 33(3) PCT.

3.5 Dependent claims 10 to 13, 23 to 32, as far as they are dependent upon claims 1 and 14, do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step.

3.6 In view of the above, the present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1, 10 to 14, 23 to 32 does

not involve an inventive step.

4 For the assessment of the present claims 23 and 24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/000562	18.01.2005	22.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07K14/195, C12N15/31, C07K16/12, C12Q1/68, A61K39/02

Applicant
AKZO NOBEL N.V.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Hix, R

Telephone No. +31 70 340-3898

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1, 10-14, 23-32

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 10-14, 23-32
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1, 10-14, 23-32
Industrial applicability (IA)	Yes:	Claims	1, 10-14, 23-32
	No:	Claims	

2. Citations and explanations

see separate sheet.

Re Item IV

Lack of unity of invention

The separate inventions/groups of invention are:

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 2: Claims 2 and 15 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 27kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 3, protein that is at least 90% homologous to SEQ ID NO: 4, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 3: Claims 3 and 16 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 62kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 5, protein that is at least 90% homologous to SEQ ID NO: 6, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 4: Claims 4 and 17 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 57kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic

acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 7, protein that is at least 90% homologous to SEQ ID NO: 8, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 5: Claims 5 and 18 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 74kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 9, protein that is at least 90% homologous to SEQ ID NO: 10, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 6: Claims 6 and 19 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 44kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 11, protein that is at least 90% homologous to SEQ ID NO: 12, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 7: Claims 7 and 20 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 43kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 13, protein that is at least 90% homologous to SEQ ID NO: 14, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 8: Claims 8 and 21 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 26/31kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 15, protein that is at least 90% homologous to SEQ ID NO: 16, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 9: Claims 9 and 22 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 101kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 17, protein that is at least 90% homologous to SEQ ID NO: 18, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

The general concept of characterizing nucleic acids which encode *Lawsonia intracellularis* proteins as using them in vaccines against *Lawsonia intracellularis* is already known from the prior art document D1: EP-A-1 219 711 (Akzo Nobel N.V.) and D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)

D1 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D2 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.

Due to the fact that the common unifying concept is known in the state of the art, there appears therefore to be no technical features in common between the different inventions involving different nucleotide and amino acid sequences, that could provide a novel and inventive unifying concept.

Consequently, the requisite unity of invention (Rule 13.1 PCT) therefore

no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the groups of claims.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Examination of :

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

1 The following **documents** are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: EP-A-1 219 711 (Akzo Nobel N.V.)

D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)

2 **NOVELTY** (Art. 33(2) PCT)

2.1 In view of the prior art cited, claims 1 and 14 and claims dependent thereon appear to be novel and meet therefore the requirements of Art.33(2) PCT, since

the nucleic and amino acid sequences SEQ ID NOs: 1 and 2 are not disclosed in the state of the art.

3 **INVENTIVE STEP** (Art. 33(3) PCT)

3.1 Documents D2 and D3 are considered to represent the most relevant state of the art. D2 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D3 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.

3.2 The subject-matter of the present application and claims 1 and 14 and claims dependent thereon involve different nucleic acid sequences and their use as immunogenic fragments as vaccines against *Lawsonia intracellularis*.

3.3 The problem may be defined as the provision of alternative nucleic acid sequences and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*.

3.4 However due to the fact that the above problem has previously been solved by the subunit vaccines of the state of the art and that there is no evidence in the description that the nucleic or amino acid sequences SEQ ID NOs: 1 and 2 actually solve the problem through initiating an effective protective immune response to *Lawsonia intracellularis*, the subject-matter of claims 1 and 14 cannot be recognized as involving an inventive step according to Article 33(3) PCT.

3.5 Dependent claims 10 to 13, 23 to 32, as far as they are dependent upon claims 1 and 14, do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step.

3.6 In view of the above, the present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1, 10 to 14, 23 to 32 does

not involve an inventive step.

4 For the assessment of the present claims 23 and 24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2005/000562	International filing date *(day/month/year)* 18.01.2005
Priority date *(day/month/year)* 22.01.2004	
International Patent Classification (IPC) or both national classification and IPC C07K14/195, C12N15/31, C07K16/12, C12Q1/68, A61K39/02	
Applicant AKZO NOBEL N.V.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Hix, R

Telephone No. +31 70 340-3898

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000562

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1, 10-14, 23-32

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 10-14, 23-32
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1, 10-14, 23-32
Industrial applicability (IA)	Yes:	Claims	1, 10-14, 23-32
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item IV

Lack of unity of invention

The separate inventions/groups of invention are:

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 2: Claims 2 and 15 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 27kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 3, protein that is at least 90% homologous to SEQ ID NO: 4, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 3: Claims 3 and 16 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 62kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 5, protein that is at least 90% homologous to SEQ ID NO: 6, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 4: Claims 4 and 17 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 57kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic

acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 7, protein that is at least 90% homologous to SEQ ID NO: 8, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 5: Claims 5 and 18 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 74kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 9, protein that is at least 90% homologous to SEQ ID NO: 10, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 6: Claims 6 and 19 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 44kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 11, protein that is at least 90% homologous to SEQ ID NO: 12, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 7: Claims 7 and 20 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 43kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 13, protein that is at least 90% homologous to SEQ ID NO: 14, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 8: Claims 8 and 21 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 26/31kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 15, protein that is at least 90% homologous to SEQ ID NO: 16, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

Invention 9: Claims 9 and 22 completely and claims 10 to 13, 23 to 32 partially.
Nucleic acid sequence encoding a 101kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 17, protein that is at least 90% homologous to SEQ ID NO: 18, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

The general concept of characterizing nucleic acids which encode *Lawsonia intracellularis* proteins as using them in vaccines against *Lawsonia intracellularis* is already known from the prior art document D1: EP-A-1 219 711 (Akzo Nobel N.V.) and D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)

D1 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D2 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.

Due to the fact that the common unifying concept is known in the state of the art, there appears therefore to be no technical features in common between the different inventions involving different nucleotide and amino acid sequences, that could provide a novel and inventive unifying concept.

Consequently, the requisite unity of invention (Rule 13.1 PCT) therefore

no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the groups of claims.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Examination of :

Invention 1: Claims 1 and 14 completely and claims 10 to 13, 23 to 32 partially.

Nucleic acid sequence encoding a 75kD *Lawsonia intracellularis* protein or a part of said nucleic acid sequence that encodes an immunogenic fragment of said protein said nucleic acid sequence, or said part thereof having at least 90% homology with the nucleic acid sequence as depicted in SEQ ID NO: 1, protein that is at least 90% homologous to SEQ ID NO: 2, live recombinant carrier, host cell, vaccine comprising said nucleic acid, use of said protein in the manufacture of a vaccine and method of preparing said vaccine, diagnostic tests involving said nucleic acid or proteins.

1 The following **documents** are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: EP-A-1 219 711 (Akzo Nobel N.V.)

D2: WO-A-0 226 250 (Arizona Board of Regents on behalf of the University of Arizona.)

2 **NOVELTY** (Art. 33(2) PCT)

2.1 In view of the prior art cited, claims 1 and 14 and claims dependent thereon appear to be novel and meet therefore the requirements of Art.33(2) PCT, since

the nucleic and amino acid sequences SEQ ID NOs: 1 and 2 are not disclosed in the state of the art.

3 **INVENTIVE STEP** (Art. 33(3) PCT)

3.1 Documents D2 and D3 are considered to represent the most relevant state of the art. D2 discloses nucleic acid sequences encoding *Lawsonia intracellularis* outer membrane proteins and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*. D3 describes vaccines against proliferative ileitis containing protective immunogenic subunits of *Lawsonia intracellularis*.

3.2 The subject-matter of the present application and claims 1 and 14 and claims dependent thereon involve different nucleic acid sequences and their use as immunogenic fragments as vaccines against *Lawsonia intracellularis*.

3.3 The problem may be defined as the provision of alternative nucleic acid sequences and immunogenic fragments for use as vaccines against *Lawsonia intracellularis*.

3.4 However due to the fact that the above problem has previously been solved by the subunit vaccines of the state of the art and that there is no evidence in the description that the nucleic or amino acid sequences SEQ ID NOs: 1 and 2 actually solve the problem through initiating an effective protective immune response to *Lawsonia intracellularis*, the subject-matter of claims 1 and 14 cannot be recognized as involving an inventive step according to Article 33(3) PCT.

3.5 Dependent claims 10 to 13, 23 to 32, as far as they are dependent upon claims 1 and 14, do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step.

3.6 In view of the above, the present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1, 10 to 14, 23 to 32 does

not involve an inventive step.

4 For the assessment of the present claims 23 and 24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.